4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 862

[Docket No. FDA-2022-N-3335]

Medical Devices; Clinical Chemistry and Clinical Toxicology Devices; Classification of the Prognostic Test for Assessment of Liver Related Disease Progression

AGENCY: Food and Drug Administration, HHS.

ACTION: Final amendment; final order.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is classifying the prognostic test for assessment of liver related disease progression into class II (special controls). The special controls that apply to the device type are identified in this order and will be part of the codified language for the prognostic test for assessment of liver related disease progression's classification. We are taking this action because we have determined that classifying the device into class II (special controls) will provide a reasonable assurance of safety and effectiveness of the device. We believe this action will also enhance patients' access to beneficial innovative devices.

DATES: This order is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The classification was applicable on August 20, 2021.

FOR FURTHER INFORMATION CONTACT: Irene Tebbs, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3526, Silver Spring, MD 20993-0002, 340-402-0283, Irene.Tebbs@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

Upon request, FDA has classified the prognostic test for assessment of liver related disease progression as class II (special controls), which we have determined will provide a

reasonable assurance of safety and effectiveness. In addition, we believe this action will enhance patients' access to beneficial innovation, in part by placing the device into a lower device class than the automatic class III assignment.

The automatic assignment of class III occurs by operation of law and without any action by FDA, regardless of the level of risk posed by the new device. Any device that was not in commercial distribution before May 28, 1976, is automatically classified as, and remains within, class III and requires premarket approval unless and until FDA takes an action to classify or reclassify the device (see 21 U.S.C. 360c(f)(1)). We refer to these devices as "postamendments devices" because they were not in commercial distribution prior to the date of enactment of the Medical Device Amendments of 1976, which amended the Federal Food, Drug, and Cosmetic Act (FD&C Act).

FDA may take a variety of actions in appropriate circumstances to classify or reclassify a device into class I or II. We may issue an order finding a new device to be substantially equivalent under section 513(i) of the FD&C Act (see 21 U.S.C. 360c(i)) to a predicate device that does not require premarket approval. We determine whether a new device is substantially equivalent to a predicate device by means of the procedures for premarket notification under section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

FDA may also classify a device through "De Novo" classification, a common name for the process authorized under section 513(f)(2) of the FD&C Act. Section 207 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) established the first procedure for De Novo classification. Section 607 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) modified the De Novo application process by adding a second procedure. A device sponsor may utilize either procedure for De Novo classification.

Under the first procedure, the person submits a 510(k) for a device that has not previously been classified. After receiving an order from FDA classifying the device into class III under

section 513(f)(1) of the FD&C Act, the person then requests a classification under section 513(f)(2).

Under the second procedure, rather than first submitting a 510(k) and then a request for classification, if the person determines that there is no legally marketed device upon which to base a determination of substantial equivalence, that person requests a classification under section 513(f)(2) of the FD&C Act.

Under either procedure for De Novo classification, FDA is required to classify the device by written order within 120 days. The classification will be according to the criteria under section 513(a)(1) of the FD&C Act. Although the device was automatically placed within class III, the De Novo classification is considered to be the initial classification of the device.

When FDA classifies a device into class I or II via the De Novo process, the device can serve as a predicate for future devices of that type, including for 510(k)s (see section 513(f)(2)(B)(i) of the FD&C Act). As a result, other device sponsors do not have to submit a De Novo request or premarket approval application to market a substantially equivalent device (see section 513(i) of the FD&C Act, defining "substantial equivalence"). Instead, sponsors can use the less-burdensome 510(k) process, when necessary, to market their device.

II. De Novo Classification

On November 4, 2020, FDA received Siemens Healthcare Diagnostics Inc.'s request for De Novo classification of the ADVIA Centaur Enhanced Liver Fibrosis. FDA reviewed the request in order to classify the device under the criteria for classification set forth in section 513(a)(1) of the FD&C Act.

We classify devices into class II if general controls by themselves are insufficient to provide reasonable assurance of safety and effectiveness, but there is sufficient information to establish special controls that, in combination with the general controls, provide reasonable assurance of the safety and effectiveness of the device for its intended use (see 21 U.S.C. 360c(a)(1)(B)). After review of the information submitted in the request, we determined that the

device can be classified into class II with the establishment of special controls. FDA has determined that these special controls, in addition to the general controls, will provide reasonable assurance of the safety and effectiveness of the device.

Therefore, on August 20, 2021, FDA issued an order to the requester classifying the device into class II. In this final order, FDA is codifying the classification of the device by adding 21 CFR 862.1622.[1] We have named the generic type of device prognostic test for assessment of liver related disease progression, and it is identified as a device intended to measure one or more analytes obtained from human samples as an aid in assessing progression of liver related disease. This device is not intended for diagnosis of any disease, for monitoring the effect of any therapeutic product, for assessing progression to hepatocellular carcinoma, or for assessing disease progression in individuals with viral hepatitis. It is also not intended for the detection of viruses, viral antigens, or antibodies to viruses.

FDA has identified the following risks to health associated specifically with this type of device and the measures required to mitigate these risks in table 1.

Table 1.--Prognostic Test for Assessment of Liver Related Disease Progression Risks and Mitigation Measures

Identified Risks	Mitigation Measures
False negative results leading to delayed assessment or treatment	Certain design verification and validation activities, including certain clinical studies; and Certain labeling information, including certain warnings and performance information
False positive results leading to unnecessary medical procedures	Certain design verification and validation activities, including certain clinical studies; and Certain labeling information, including certain warnings and performance information

FDA has determined that special controls, in combination with the general controls, address these risks to health and provide reasonable assurance of safety and effectiveness. For a device to fall within this classification, and thus avoid automatic classification in class III, it

[1] FDA notes that the "ACTION" caption for this final order is styled as "Final amendment; final order," rather than "Final order." Beginning in December 2019, this editorial change was made to indicate that the document "amends" the Code of Federal Regulations. The change was made in accordance with the Office of Federal Register's (OFR) interpretations of the Federal Register Act (44 U.S.C. chapter 15), its implementing regulations (1 CFR 5.9 and parts 21 and 22), and the Document Drafting Handbook.

would have to comply with the special controls named in this final order. The necessary special controls appear in the regulation codified by this order. This device is subject to premarket notification requirements under section 510(k) of the FD&C Act.

III. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Paperwork Reduction Act of 1995

This final order establishes special controls that refer to previously approved collections of information found in other FDA regulations and guidance. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3521). The collections of information in 21 CFR part 860, subpart D, regarding De Novo classification have been approved under OMB control number 0910-0844; the collections of information in 21 CFR part 814, subparts A through E, regarding premarket approval, have been approved under OMB control number 0910-0231; the collections of information in part 807, subpart E, regarding premarket notification submissions, have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 820, regarding quality system regulation, have been approved under OMB control number 0910-0073; and the collections of information in 21 CFR parts 801and 809, regarding labeling, have been approved under OMB control number 0910-0485.

List of Subjects in 21 CFR Part 862

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 862 is amended as follows:

PART 862--CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES

1. The authority citation for part 862 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 360l, 371.

2. Add § 862.1622 to subpart B to read as follows:

§ 862.1622 Prognostic test for assessment of liver related disease progression.

(a) *Identification*. A prognostic test for assessment of liver related disease progression is intended to measure one or more analytes obtained from human samples as an aid in assessing progression of liver related disease. This device is not intended for diagnosis of any disease, for monitoring the effect of any therapeutic product, for assessing progression to hepatocellular carcinoma, or for assessing disease progression in individuals with viral hepatitis. It is also not intended for the detection of viruses, viral antigens, or antibodies to viruses.

(b) *Classification*. Class II (special controls). The special controls for this device are:

(1) Design verification and validation must include clinical validation data providing:

(i) Information demonstrating clinical performance in a population of patients with liver disease for the different risk categories (e.g., at lower risk, at higher risk) for progression of their disease using well characterized clinical specimens representing the intended use population collected from multiple intended clinical sites, or an alternative study design determined to be appropriate by FDA.

(ii) Information demonstrating that the outcomes measured and the length of followup are clinically relevant for the progression of the specified liver disease.

(iii) Information demonstrating that the clinical criteria for determining whether the target disease is present and that the exclusion and inclusion criteria for subjects who have the target disease are appropriate.

(iv) Information demonstrating test performance of the complete test system, including any sample collection and processing steps.

(v) Information, provided or referenced, generated in samples from non-diseased individuals, that demonstrate the upper and lower reference intervals for the output provided by the device.

(2) The labeling required under 21 CFR 809.10(b) must include:

(i) A warning statement that test results are not intended to diagnose disease or for monitoring the effect of any therapeutic product.

(ii) A warning statement that test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including information obtained by alternative methods, and clinical evaluation, as appropriate.

(iii) A warning statement that describes any limitations on the clinical interpretation(s) of the test results.

(iv) Detailed information on device performance, including any limitations to the data generated in the clinical study(ies) and information on device performance in relevant subgroups (e.g., severity of liver disease at the beginning of the observation period) observed in the clinical study(ies).

(v) Information on the analytical performance of the device, including demonstration of reproducibility across multiple sites and multiple reagent lots, or an alternative reproducibility study design determined to be appropriate by FDA.

Dated: January 6, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023-00480 Filed: 1/13/2023 8:45 am; Publication Date: 1/17/2023]